Mathematical Models of Ewing Sarcoma Incidence Can Estimate the Frequency of Sarcomagenic EWSR1 gene fusion events

Nakul Shankar, MD[1], Michael A. Arnold, MD, PhD, FCAP[1,2]
[1]Department of Pathology, University of Colorado, Anschutz Medical Campus.
[2]Department of Pathology and Laboratory Medicine, Children's Hospital Colorado, Anschutz Medical Campus

University of Colorado Anschutz Medical Campus

Children's Hospital Colorado

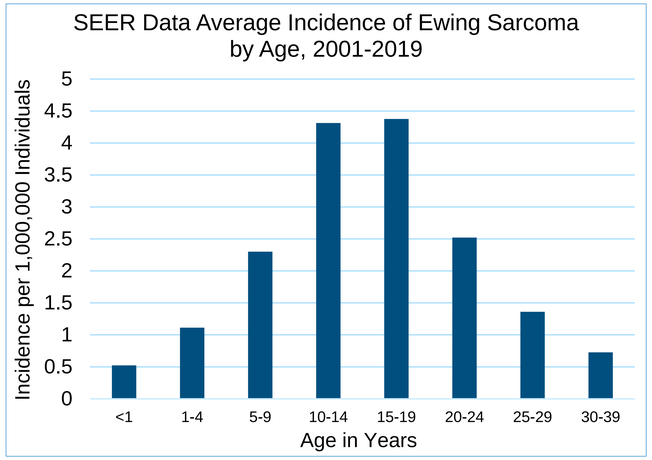
BACKGROUND

The incidence of Ewing sarcoma peaks in teenagers. Typical models for the progression to cancers that occur commonly later in adulthood cannot account for the observed incidence of Ewing sarcoma in adolescents and young adults. We present mathematical models of different hypotheses that could explain the observed age distribution of Ewing sarcoma and can also provide insights into the stem cell biology that might be driving the observed incidence of Ewing sarcoma. These models could be adapted to explain the incidence of other childhood cancer types.

DESIGN

We extracted incidence data for Ewing sarcoma from the National Childhood Cancer Registry Explorer published by the National Cancer Institute. We calculated an average incidence of Ewing sarcoma per 1,000,000 individuals for data from 2001 to 2019. The number of sarcomagenic events (E) was calculated for each age cohort as the product the population size (P) of 1,000,000 individuals, years in age group (Y), the relative number of susceptible stem cells present in individuals under 1 year of age (C) and of the risk of a sarcomagenic EWSR1 gene fusion occurring in the number of susceptible stem cells present in an individual under 1 year of age (R) during 1 year of time.

RESULTS



Hypotheses:

1) The risk of a sarcomagenic event in a given cell is constant and variation in the rate of Ewing sarcoma by age results from variation in the population of susceptible stem cells (C).
2) The risk of a sarcomagenic event increases linearly over time and variation in the rate of Ewing sarcoma by age results from variation in the population of susceptible stem cells (C).
3) The incidence of Ewing sarcoma can be described by random events that only result in sarcomas in individuals with rare genetic combinations. The occurrence of these events can be described by a Gaussian distribution.

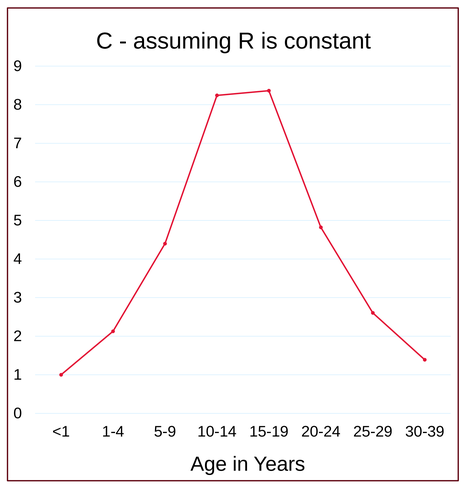
$$E=CRYP \qquad C=\frac{E}{RYP}$$

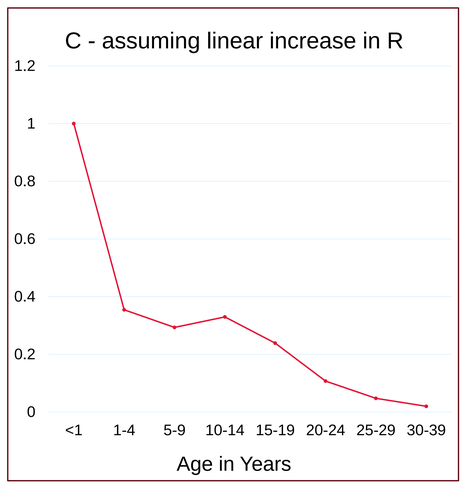
<1y: $0.523=1 \times R \times 1 \times 1x10^{6}$

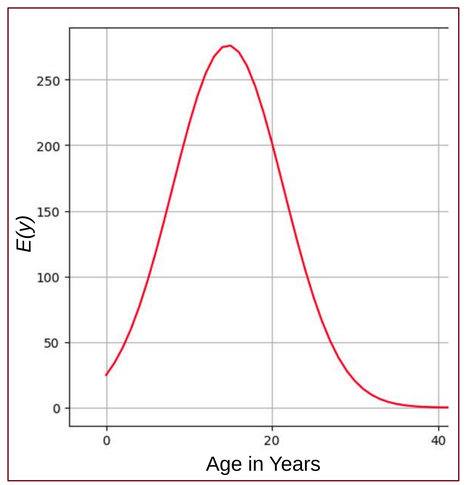
$R=5.23 \times 10^{-7}$

$$E(y) = \left(1 \,/\, \left(N(y) * \sigma * sqrt(2\pi)\right)\right) * e\text{^}\left(-\left(ln\left(N(y)\right) - \mu\right)^2 \,/\, \left(2\sigma^2\right)\right)$$

N(y) is the number of cases at age y
μ is the mean of the natural logarithm of the distribution
σ is the standard deviation of the natural logarithm of the distribution







CONCLUSIONS

Variations in the rate of Ewing sarcoma incidence by age could be explained by fluctuations in the population of susceptible stem cells capable of undergoing sarcomagenesis. Models of this process can be refined by data quantifying the population of cells capable of becoming Ewing sarcoma throughout life. We believe our mathematical models can explain why the incidence of pediatric cancers peaks in specific age ranges, and that similar models can be applied to understanding other pediatric cancer types.